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【 CASE REPORT 】

# Development of Polyneuropathy, Organomegaly, Endocrinopathy, M Protein, and Skin Changes Syndrome after Conversion from Plasmacytoma of Bone to Multiple Myeloma

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**Abstract:**

A 36-year-old man developed polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome after conversion from solitary plasmacytoma of bone to multiple myeloma. Twenty-four days following the neurological onset, he lost his independent walking ability. The level of serum vascular endothelial growth factor (VEGF) at diagnosis was 5,250 pg/mL. Three months after initiating treatment, he regained his independent walking ability in line with a reduction in the elevated serum VEGF level. Due to their genomic instability gained during conversion, myeloma cells may overproduce humoral factors and cytokines, possibly contributing to the development of neuropathy as well as the production of VEGF.

**Key words:** POEMS syndrome, vascular endothelial growth factor, conversion from a solitary plasmacytoma of bone to multiple myeloma

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## Introduction

Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome is a rare cause of demyelinating and axonal mixed polyneuropathy. It is accompanied by the overproduction of vascular endothelial growth factor (VEGF) and plasma cell dyscrasia (1-4). The other humoral factors, including interleukin-6 (IL-6) and interleukin-1β (IL-1β), are probably related to the development of POEMS syndrome (4). However, the detailed pathophysiology of POEMS syndrome has not been fully revealed yet.

Both solitary plasmacytoma of bone (SPB) and multiple myeloma (MM) are forms of plasma cell dyscrasia, and 50-70% of SPB cases convert to MM (5, 6). During the conversion from SPB to MM, plasma cells gain genome instability, and myeloma cells gain genomic diversity during the proliferation (7, 8).

The clinical course of neuropathy in POEMS syndrome is usually chronic. The median period from the disease onset to being incapable of walking independently is 9.5 months (9). Thus, cases with POEMS syndrome showing acute progression are rare.

We herein report a case of POEMS syndrome with acute progression of polyneuropathy; the patient lost his independent walking ability within 24 days of the disease onset. Furthermore, this is the first reported case of POEMS syndrome that developed after the diagnosis of conversion from SPB to MM. Overproduced VEGF and other humoral factors related to genomic diversity of myeloma cells during the conversion might have played roles in the atypical course of the neuropathy.

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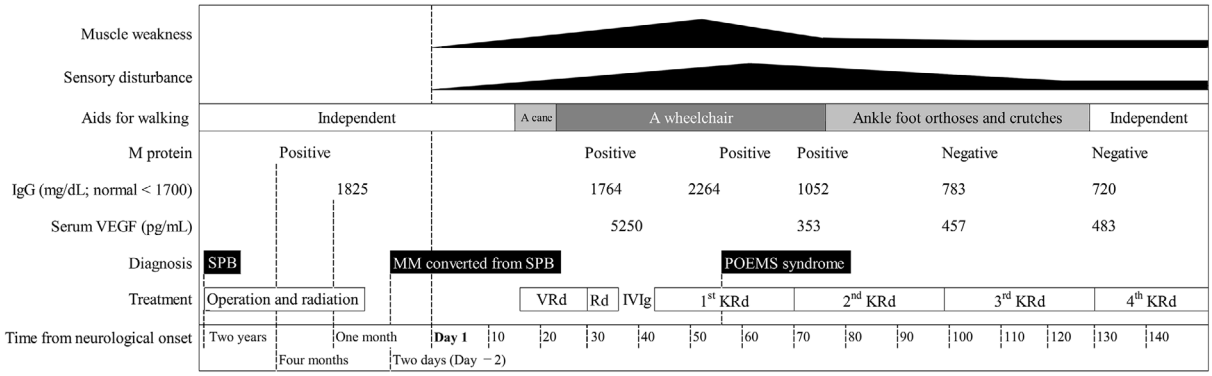


**Figure 1. Clinical course of the case. The time course of the neurological symptoms and aids for walking is shown in relation to the diagnosis, treatment, and laboratory data, including serum vascular endothelial growth factor (VEGF). SPB: solitary plasmacytoma of bone, MM: multiple myeloma, VRd: bortezomib, lenalidomide, and dexamethasone, Rd: lenalidomide and dexamethasone, KRd: carfilzomib, lenalidomide, and dexamethasone**

## Case Report

A 36-year-old man presented with symmetric weakness of the distal lower limbs and dysesthesia in the fingers one day (day 1=onset of neurological symptoms) (Fig. 1). He had no remarkable medical or family history of neurological diseases. He rarely drank alcohol and had never smoked.

Two years before day 1, he had been diagnosed with SPB in the second lumbar vertebra (L2). SPB had been treated by total en bloc spondylectomy and radiation therapy. Four months before day 1, his serum M protein turned positive. A month before day 1, immunoglobulin G (IgG) levels had elevated to 1,825 mg/dL (normal <1,700). Two days before day 1, he had been diagnosed with MM converted from SPB. The diagnosis was based on the osteolytic lesions of the cranial and limb bones shown by bone radiography, and $^{18}$F-fluorodeoxyglucose-positron emission tomography (FDG-PET) and laboratory examination results indicating IgG-lambda monoclonal gammopathy. He was able to walk at least 200 m continuously and independently.

On day 1, he presented with symmetric weakness of the extensor and flexor of the ankle joints and tingling in the fingers. Subsequently, the tingling appeared in both toes on day 3. Although bortezomib, lenalidomide, and dexamethasone (VRd) therapy was performed for MM on day 17, his symptoms showed acute progression. He needed a cane to walk on day 17 and became a wheelchair user on day 24. He was referred to the neurology department on day 29 and was admitted to our hospital on the same day.

On admission (day 29), a physical examination revealed edema in the lower limbs, skin pigmentation, and hemangiomas. Neurological examinations showed symmetrical muscle weakness in the four limbs, which was graded as 4/5 in the upper limbs, 3/5 in the proximal lower limbs, and 1-2/5 in the distal lower limbs on the medical research council (MRC) scale. Deep tendon reflexes were absent in the four limbs, and plantar reflexes were normal bilaterally. Touch sensation was symmetrically decreased to 8/10 in hands and 4/10 in feet in contrast to that in the chest, which was used as a control, but pain sensation was spared. Vibration and joint position sensations were diminished in the ankles and toes, respectively, and mild tingling in the fingers and toes persisted. No symptoms associated with cranial or autonomic nerve involvement were noted.

Blood examinations showed almost normal findings, except for serum IgG-lambda monoclonal gammopathy. The levels of hemoglobin A1c, vitamins B1 and B12, and folic acid were within normal range, and test results for angiotensin-converting enzyme (ACE), anti-SS-A antibodies, and antineutrophil cytoplasmic antibodies were all negative. Endocrine tests showed no significant abnormalities. Liquor examinations showed an elevated protein level (94 mg/dL), but pleocytosis and elevation of the ACE level were absent, and cytology was negative. Whole-body bone radiography showed a sclerotic lesion on the right femur and multiple lytic lesions on the cranial and limb bones. $^{18}$F-FDG-PET showed abnormal uptake in the bilateral humeri, femur, and left scapula. Abdominal computed tomography revealed hepatosplenomegaly. Thoracolumbar magnetic resonance imaging showed normal findings except for postoperative changes.

The nerve conduction studies (NCS) on day 30 (Table) showed demyelination dominant mixed polyneuropathy prominent in the lower limbs. The median, ulnar, and tibial motor nerves showed prolonged distal latency, and all of the tested motor nerves showed prominent decreases in conduction velocities. The peroneal nerve showed a low amplitude of compound muscle action potential (CMAP). F-waves of median and tibial nerves were not recordable. The median and ulnar sensory nerves showed decreased conduction velocities and action potentials, and the sural sensory nerve action potential (SNAP) was not recordable due to the edema in the feet. Conduction block was absent. Based on these findings, bortezomib was discontinued from day 30 onward because it carried a risk of having deteriorated the neuropa-

**Table.** **Nerve Conduction Studies Performed before and after Initiating Treatment.**

| Day | 30 (Before treatment) | 129 (After initiating treatment) | |
|---|---|---|---|
| Motor | | | Normal limit |
| Median (wrist, elbow) | | | |
| Distal latency (ms) | 4.5 | 4.4 | <3.5 |
| CMAP amplitude, distal/proximal (mV) | 14.9/12.2 | 18.6/16.4 | >10 |
| Conduction velocity (m/s) | 36.4 | 42 | >54 |
| F-wave latency (ms) | NR | 34.7 | <27 |
| Ulnar (wrist, elbow) | | | |
| Distal latency (ms) | 4.2 | 4.1 | <2.9 |
| CMAP amplitude, distal/proximal (mV) | 13.3/10.3 | 9.5/7.5 | >10 |
| Conduction velocity (m/s) | 40.4 | 41.8 | >61 |
| Peroneal (ankle, head of fibula, popliteal) | | | |
| Distal latency (ms) | 4.9 (5.0) | NR | <5.0 |
| CMAP amplitude, distal/proximal (mV) | 1.9/0.5/0.5 (4) | | >4 |
| Conduction velocity (m/s) | 26 | | >42 |
| Tibial (ankle, popliteal fossa) | | | |
| Distal latency (ms) | 5.2 | ND | <5.1 |
| CMAP amplitude, distal/proximal (mV) | 9.1/2.4 | | >10 |
| Conduction velocity (m/s) | 35.5 | | >43 |
| F-wave latency (ms) | NR | ND | |
| Sensory | | | Normal limit |
| Median | | | |
| SNAP amplitude (μV) | 8.7 | 4.2 | >10 |
| Conduction velocity (m/s) | 43.3 | 55.9 | >51 |
| Ulnar | | | |
| SNAP amplitude (μV) | 1.8 | 5.8 | >10 |
| Conduction velocity (m/s) | 38.4 | 49.3 | >46 |
| Sural | | | |
| SNAP amplitude (μV) | NR | 11.2 | >6 |
| Conduction velocity (m/s) | | 45.8 | >47 |

CMAP: compound muscle action potential, SNAP: sensory nerve action potential, NR: not recordable, ND: no data

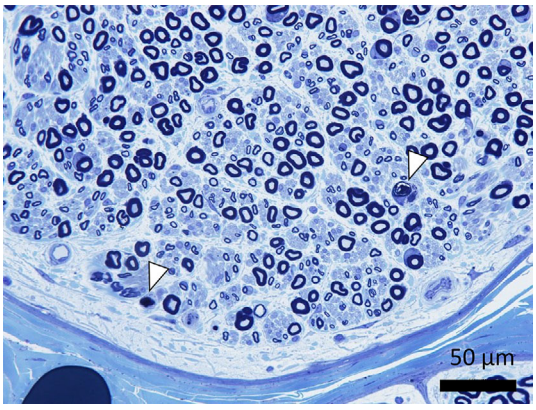


**Figure 2.** **Photomicrograph of the sural nerve (Epon-embedded section stained with toluidine blue). Prominent edema beneath the perineurium, slightly decreased myelinated fiber density, and scattered acute axonal changes suggested by myelin ovoid formation (white arrowheads) can be seen. Microvascular changes were not present. Scale bar=50 μm.**

thy.

We considered POEMS syndrome showing an atypical course of neuropathy as the diagnosis, but to exclude atypical sarcoidosis or vasculitis, a sural nerve biopsy was performed on day 38. Light microscopy showed slightly decreased myelinated fiber density and scattered acute axonal changes with prominent edema but did not show findings suggesting sarcoidosis or vasculitis. These findings were consistent with those of POEMS syndrome (Fig. 2), though light and electron microscopy showed no microvascular changes, such as vascular endothelial cell swelling, and electron microscopy showed no uncompacted myelin lamellae. Congo-Red Methyl-violet staining showed no amyloid deposition.

Intravenous immunoglobulin (IVIg: 0.4 g/kg/day for 5 days) was administered from day 38 onward. However, the neurological symptoms continued to deteriorate. In contrast, after the first course of carfilzomib, lenalidomide, and dexamethasone (KRd) therapy was initiated on day 43, muscle weakness and sensory disturbance began to improve on day 52 and day 61, respectively. A prominently elevated serum VEGF level of 5,250 pg/mL evaluated on day 35 was reported on day 56. Based on the elevated serum VEGF level, polyneuropathy, plasma cell dyscrasia, a sclerotic bone lesion, hepatosplenomegaly, edema, skin pigmentation, and hemangiomas, we diagnosed the patient with POEMS syn-

drome (4).

After the first course of KRd therapy, the serum VEGF level decreased to 353 pg/mL, and the IgG level decreased to the normal range. The second to fourth courses of KRd therapy were administered every four weeks starting from day 70. After the second course, M protein became negative, and the low serum VEGF level was maintained (457 pg/mL). He was able to walk with ankle foot orthoses and crutches on day 76. After the third course, on day 127, the patient was able to walk independently, and a hematologic complete response was achieved. The low serum VEGF level was maintained (483 pg/mL).

The NCS on day 129 (Table) compared to that on day 30 showed no apparent improvement in distal latencies, CMAP, or conduction velocities of the median or ulnar motor nerves. CMAP of the ulnar nerve was decreased, and that of the peroneal nerve became unrecordable. The median SNAP was decreased, but the median and ulnar sensory nerves showed normalized conduction velocities, and the ulnar SNAP was increased, and the sural SNAP became recordable.

The improvement of the neurological symptoms was maintained following the administration of high-dose melphalan with autologous stem cell transplantation, which was administered after the KRd therapy.

## Discussion

We encountered a case of POEMS syndrome that developed neuropathy after conversion from SPB to MM. Although the hematological findings suggested the conversion from SPB to MM four months before the onset of neurological symptoms, the progression of neuropathy after the onset was acute. The neurophysiological findings suggested demyelination dominant mixed polyneuropathy, and pathology of the sural neve showed mild axonal changes with prominent edema. In contrast to IVIg, which was administered based on a previous report (10) on the effectiveness of IVIg for POEMS syndrome, KRd therapies were clearly effective. Along with the reduction in the serum VEGF levels, the patient regained his independent walking ability within three months. Although the improvement of NCS findings after initiating treatment was partial, this favorable clinical response to the treatment suggests that the neuropathy had mainly been caused by demyelination. The demyelination was probably in the proximal portions of peripheral nerves rather than axonal degeneration, which a sural nerve biopsy suggested.

Of interest, the development of polyneuropathy in our case coincided with the conversion from SPB to MM. To our knowledge, this is the first case of POEMS syndrome that developed after conversion from SPB to MM. During the conversion from SPB to MM, plasma cells gain genome instability, and myeloma cells proliferate with cytogenetic diversity based on chromosomal and genetic abnormalities, epigenomic modifications, and modified bone marrow microenvironment (7, 8). During conversion, myeloma cells produce various humoral factors and cytokines, and humoral factors (including IL-6 and IL-1β) may contribute to the production of VEGF (11).

The mechanisms underlying the neuropathy associated with POEMS syndrome have not been fully elucidated. It has been hypothesized that VEGF increases vascular permeability (12) and induces edema and deposition of M protein in the peripheral nerves (13), which may induce nervous injury. Indeed, in this case, the serum VEGF level before treatment was extremely high (5,250 pg/mL). However, humoral factors and cytokines other than VEGF were presumed to be activated in this case. The present findings suggest the need to consider factors other than VEGF as being involved in the mechanisms underlying neuropathy associated with POEMS syndrome.

In conclusion, we reported a case of POEMS syndrome after conversion from SPB to MM. Overproduced VEGF and other humoral factors related to genomic diversity of myeloma cells during the conversion might have played roles in the development of neuropathy. The further accumulation of cases will be needed to clarify the detailed mechanisms underlying the development of POEMS syndrome after conversion from SPB to MM.

All informed consent was obtained from the subject.

**The authors state that they have no Conflict of Interest (COI).**

### References


1. Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine **59**: 311-322, 1980.
2. Miralles GD, O'Fallon JR, Talley NJ. Plasma-cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. N Engl J Med **327**: 1919-1923, 1992.
3. Suichi T, Misawa S, Beppu M, et al. Prevalence, clinical profiles, and prognosis of POEMS syndrome in Japanese nationwide survey. Neurology **93**: e975-e983, 2019.
4. Dispenzieri A. POEMS syndrome: 2019 update on diagnosis, risk-stratification, and management. Am J Hematol **94**: 812-827, 2019.
5. Knobel D, Zouhair A, Tsang RW, et al. Prognostic factors in solitary plasmacytoma of the bone: a multicenter Rare Cancer Network study. BMC Cancer **6**: 118, 2006.
6. Waal EGM, Leene M, Veeger N, et al. Progression of a solitary plasmacytoma to multiple myeloma. A population-based registry of the northern Netherlands. Br J Haematol **175**: 661-667, 2016.
7. Egan JB, Shi CX, Tembe W, et al. Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides. Blood **120**: 1060-1066, 2012.
8. Neuse CJ, Lomas OC, Schliemann C, Shen YJ, Manier S, Bustoros M. Genome instability in multiple myeloma. Leukemia **34**: 2887-2897, 2020.
9. Isose S, Misawa S, Kanai K, et al. POEMS syndrome with Guillan-Barré syndrome-like acute onset: a case report and review of neurological progression in 30 cases. J Neurol Neurosurg Psy-

chiatry **82**: 678-680, 2011.

**10.** Terracciano C, Fiore S, Doldo E, et al. Inverse correlation between VEGF and soluble VEGF receptor 2 in POEMS with AIDP responsive to intravenous immunoglobulin. Muscle Nerve **42**: 445-448, 2010.

**11.** Soubrier M, Dubost JJ, Serre AF, et al. Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. Arthritis Rheum **40**: 786-787, 1997.

**12.** Watanabe O, Maruyama I, Arimura K, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve **21**: 1390-1397, 1998.

**13.** Braun PE, Frail DE, Latov N. Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. J Neurochem **39**: 1261-1265, 1982.